

10 20 30 40 50 60  
 GTTGTGCTG TGGCTGATAG CCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG  
 70 80 90 100 110 120  
 ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAAGTC  
 130 140 150 160 170 180  
 AACCCAGACCA CCTTATAACCA GCGTTATGAG ATCAAGATGTA CCAAGATGTA TAAAGGGTTC  
 190 200 210 220 230 240  
 CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTG  
 250 260 270 280 290 300  
 TGCGGATACT TCCACAGGTC CCACAAACCGC AGCGAGGAGT TTCTCATATTGC TGGAAAACTG  
 C1  
 C2  
 310 320 330 340 350 360  
 CAGGATGGAC TCTTGCACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC  
 370 380 390 400 410 420  
 TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTTG GCTGTGAGGA ATGCACAGTG  
 430 440 450 460 470 480  
 TTTCCCTGTT TATCCATCCC CTGCAAACGT CAGAGTGGCA CTCATTGCTT GTGGACGGAC  
 490 500 510 520 530 540  
 CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCCTG CCTGCCTCGG  
 550 560 570 580 590 600  
 GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA  
 610 620 630 640 650 660  
 GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCATCTT CTTCCGGACA  
 670 680 690 700  
 ATGAAATAAA GAGTTACAC CCAGCAAAAA AAAAAAGGAA TTC--

Please replace the paragraph [018], with the following paragraph:

C2  
 --[018] A second preferred DNA sequence has been discovered which has an additional nucleotide sequence 5' to the initiator sequence. This sequence, which contains as the eighty-second through four-hundred-thirty-second nucleotides nucleotides 1 through 351 of the first preferred sequence set forth above, has the following nucleotide sequence (SEQ ID No: 6):

10 20 30 40 50 60  
 GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT

70 80 90 100 110 120  
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC  
  
130 140 150 160 170 180  
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG  
  
190 200 210 220 230 240  
TTCGTGGGGA CACCAGAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG  
  
250 260 270 280 290 300  
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC  
  
310 320 330 340 350 360  
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG  
  
370 380 390 400 410 420  
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCAC TACCTG CAGTTCTGTG  
  
430  
GCTCCCTGGA AC--

Please replace the paragraph [019], with the following paragraph:

--[019] A third preferred DNA sequence which incorporates the 5' region of the second preferred sequence and the 3' sequence of the first preferred sequence, has the following nucleotide sequence (SEQ ID No: 7):

10 20 30 40 50 60  
GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT  
  
70 80 90 100 110 120  
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC  
  
130 140 150 160 170 180  
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG  
  
190 200 210 220 230 240  
TTCGTGGGGA CACCAGAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG  
  
250 260 270 280 290 300  
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC  
  
310 320 330 340 350 360  
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG  
  
370 380 390 400 410 420  
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCAC TACCTG CAGTTCTGTG

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430            440            450            460            470            480  
 GCTCCCTGGA ACAGCCTGAG CTTAGCTCAG CGCCGGGGCT TCACCAAGAC CTACACTGTT  
  
 490            500            510            520            530            540  
 GGCTGTGAGG AATGCACAGT GTTTCCCTGT TTATCCATCC CCTGCAAACACT GCAGAGTGGC  
  
 550            560            570            580            590            600  
 ACTCATTGCT TGTGGACGGA CCAGCTCCTC CAAGGCTCTG AAAAGGGCTT CCAGTCCCCT  
  
 610            620            630            640            650            660  
 CACCTTGCCT GCCTGCCCTCG GGAGCCAGGG CTGTGCACCT GGCAGTCCCT GCGGTCCCAG  
  
 670            680            690            700            710            720  
 ATAGCCTGAA TCCTGCCCGG AGTGGAAAGCT GAAGCCTGCA CAGTGTCCAC CCTGTTCCCA  
  
 730            740            750            760            770            780  
 CTCCCATCTT TCTTCGGAC AATGAAATAA AGAGTTACCA CCCAGCAAAA AAAAAAAGGA--

C3  
cont

Please replace the paragraph [030] with the following paragraph:

--[030] A first preferred portable DNA sequence of the present invention has a nucleotide sequence SEQ ID No: 5 as follows:

10            20            30            40            50            60  
 GTTGTGCTG TGGCTGATAG CCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG  
  
 70            80            90            100          110          120  
 ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAACGTC  
  
 130          140          150          160          170          180  
 AACCAAGACCA CCTTATACCA GCGTTATGAG ATCAAGATGA CCAAGATGTA TAAAGGGTTC  
  
 190          200          210          220          230          240  
 CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTC  
  
 250          260          270          280          290          300  
 TGCGGATACT TCCACAGGTC CCACAACCGC AGCGAGGAGT TTCTCATTGC TGGAAAATG  
  
 310          320          330          340          350          360  
 CAGGATGGAC TCTTGCACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC  
  
 370          380          390          400          410          420  
 TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTTG GCTGTGAGGA ATGCACAGTG  
  
 430          440          450          460          470          480  
 TTTCCCTGTT TATCCATCCC CTGCAAACGT CAGAGTGGCA CTCATTGCTT GTGGACGGAC  
  
 490          500          510          520          530          540  
 CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCCTG CCTGCCTCGG

C4

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550 560 570 580 590 600  
GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA  
  
610 620 630 640 650 660  
GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCCATCTTT CTTCCGGACA  
  
670 680 690 700  
ATGAAATAAA GAGTTACCAAC CCAGCAAAAAA AAAAAAAGGAA TTC--

Please insert after [030], the following new paragraph:

--[030A] The first preferred portable DNA sequence encodes a metalloproteinase inhibitor having, as a mature protein, the amino acid sequence SEQ ID No: 1 of Table 1 (using the three letter abbreviations for amino acids). The amino acid at position +1 is cysteine (Cys). The amino acid at position +184 is alanine (Ala). As seen in the other preferred portable DNA sequences described below, the DNA sequence encoding a metalloproteinase inhibitor may also encode leader sequences. The leader sequences may be designated by negative numbers beginning with -1.

TABLE 1

+184 SEQ ID NO: 1--

Please replace paragraph [031], with the following paragraph:

--[031] A second preferred portable DNA sequence of the present invention has the following nucleotide sequence (SEQ ID No: 6):

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10 20 30 40 50 60  
GGCCATGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT

70 80 90 100 110 120  
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC

130 140 150 160 170 180  
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG

190 200 210 220 230 240  
TTCGTGGGA CACCAGAAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG

250 260 270 280 290 300  
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC

310 320 330 340 350 360  
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG

370 380 390 400 410 420  
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCGTG

430  
GCTCCCTGGA AC--

Please replace paragraph [033], with the following paragraph:

--[033] A third preferred portable DNA sequence has the nucleotide sequence  
(SEQ ID No: 7):

10 20 30 40 50 60  
GGCCATGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT

70 80 90 100 110 120  
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC

130 140 150 160 170 180  
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG

190 200 210 220 230 240  
TTCGTGGGA CACCAGAAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG

250 260 270 280 290 300  
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC

310 320 330 340 350 360  
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG

370 380 390 400 410 420  
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCGTG

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430 440 450 460 470 480  
GCTCCCTGGA ACAGCCTGAG CTTAGCTCAG CGCCGGGGCT TCACCAAGAC CTACACTGTT

490 500 510 520 530 540  
GGCTGTGAGG AATGCACAGT GTTCCCTGT TTATCCATCC CCTGCAAAC GCAGAGTGGC

550 560 570 580 590 600  
ACTCATTGCT TGTGGACGGA CCAGCTCCTC CAAGGCTCTG AAAAGGGCTT CCAGTCCCGT

610 620 630 640 650 660  
CACCTTGCCT GCCTGCCCTCG GGAGCCAGGG CTGTGCACCT GGCAGTCCCT GCGGTCCCAG

670 680 690 700 710 720  
ATAGCCTGAA TCCTGCCCGG AGTGGAAAGCT GAAGCCTGCA CAGTGTCCAC CCTGTTCCCA

730 740 750 760 770 780  
CTCCCATCTT TCTTCGGAC AATGAAATAA AGAGTTACCA CCCAGCAAAA AAAAAAAGGA--

C7  
Cond

Please paragraph [059], with the paragraph:

--[059] It is anticipated that translation of mRNA coding for the metalloproteinase inhibitor in yeast will be more efficient with the preferred codon usage of yeast than with the sequence present in pUC8-Fic, as identified in Example 2, which has been tailored to the prokaryotic bias. For this reason, the portion of the 5' end of the portable DNA sequence beginning at the *Tth111I* site is preferably resynthesized. The new sequence favors the codons most frequently used in yeast. This new sequence preferably has the following nucleotide sequence:

HgiAI  
(SEQ ID No: 8) 5' GAT CCG TGC ACT TGT GTT CCA CCA CAC  
(SEQ ID No: 9) GC ACG TGA ACA CAA GGT GGT GTG  
  
CCA CAA ACT GCT TTC TGT AAC TCT GAC C  
GGT GTT TGA CGA AAG ACA TTG AGA CTG GA 3'--

Please replace paragraph [075], with the following paragraph:

--[075] In this method, the portable DNA sequences are those synthetic or naturally-occurring polynucleotides described above. In a preferred embodiment of the

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present method, the portable DNA sequence has the nucleotide sequence SEQ ID No: 5 as follows:

10            20            30            40            50            60  
GTTGTTGCTG TGGCTGATAG CCCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG

70            80            90            100          110          120  
ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAAGTC

130          140          150          160          170          180  
AACCAGACCA CCTTATACCA GCGTTATGAG ATCAAGATGA CCAAGATGTA TAAAGGGTTC

190          200          210          220          230          240  
CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTC

C9            250          260          270          280          290          300  
TGCGGATACT TCCACAGGTC CCACAACCGC AGCGAGGAGT TTCTCATATTGC TGGAAAACTG

310          320          330          340          350          360  
CAGGATGGAC TCTTGCACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC

370          380          390          400          410          420  
TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTTG GCTGTGAGGA ATGCACAGTG

430          440          450          460          470          480  
TTTCCCTGTT TATCCATCCC CTGCAAACGT CAGAGTGGCA CTCATTGCTT GTGGACGGAC

490          500          510          520          530          540  
CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCCTG CCTGCCTCGG

550          560          570          580          590          600  
GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA

610          620          630          640          650          660  
GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCCATCTTT CTTCCGGACA

670          680          690          700  
ATGAAATAAA GAGTTACCAC CCAGCAAAAA AAAAAAGGAA TTC--

Please replace paragraph [084], with the following paragraph:

--[084] In certain circumstances, the metalloproteinase inhibitor will assume its proper, active structure upon expression in the host microorganism and transport of the protein through the cell wall or membrane into the periplasmic space. This will generally occur if DNA coding for an appropriate leader sequence has been linked to the DNA

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1300 I Street, NW  
Washington, DC 20005  
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C10

*C16*  
*cont*

coding for the recombinant protein. The preferred metalloproteinase inhibitors of the present invention will assume their mature, active form upon translocation out of the inner cell membrane. The structures of numerous signal peptides have been published, for example by Marion E.E. Watson in Nuc. Acid Res. 12: 5145-5164, 1984, specifically incorporated herein by reference. It is intended that these leader sequences, together with portable DNA, will direct intracellular production of a fusion protein which will be transported through the cell membrane and will have the leader sequence portion cleaved upon release from the cell.--

Please replace paragraph [0104], with the following paragraph:

--[0104] The structure of FIBAC A is

(SEQ ID No: 10) GA TCC GCG ATC GGA GTG TAA GAA ATG TGC ACT  
(SEQ ID No: 11) G CGC TAG CCT CAC ATT CTT TAC ACG TGA  
  
*C11*  
TGC GTT CCG CCG CAT CCG CAG ACT GCT TTC  
ACG CAA GGC GGC GTA GGC GTC TGA CGA AAG  
  
TGC AAC TCT GAC C  
ACG TTG AGA CTG GA--

Please replace paragraph [0106], with the following paragraph:

*C12*  
--[0106] Component oligonucleotide FA1 (SEQ ID No: 12) is:  
GATCC GCGAT CGGAG TGTAA GAAAT GTGCA CTTGC--

Please replace paragraph [0107], with the following paragraph:

*C13*  
--[0107] Component oligonucleotide FA2 (SEQ ID No: 13) is:  
GGAACG CAAGT GCACA TTTCT TACAC TCCGA TCGCG--

Please replace paragraph [0108], with the following paragraph:

*C14*  
--[0108] Component oligonucleotide FA3 (SEQ ID No: 14) is:  
GTTC CGCCG CATCC GCAGA CTGCT TTCTG CAACT CTGAC C--

Please replace paragraph [0109], with the following paragraph:

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C15

--[0109] Component oligonucleotide FA4 (SEQ ID No: 15) is:  
AGGTC AGAGT TGCAG AAAGC AGTCT GCGGA TGCGG C--

Please replace paragraph [0112], with the following paragraph:

C16

--[0112] Linker A1 (SEQ ID No: 16) is: AATTGGCAG--

Please replace paragraph [0113], with the following paragraph:

C17

--[0113] Linker A2 (SEQ ID No: 17) is: TCGACTGCC--

Please replace paragraph [0116], with the following paragraph:

--[0116] The sequence of the sense strand (SEQ ID No: 18) is:

10	20	30	40	50	60					
GAATT	CGATA	TCTCGTTGGA	GATATT	CATG	ACGTATT	TTTG	GATGATA	AACG	AGGCGCA	AAA
E	T	E			F		M	H		
C	A	C			O		N	H		
O	Q	O			K		L	A		
1	1	5			1		1	1		

C18

70	80	90	100	110	
AATGAAAAAAG	ACAGCTATCG	CGATCGCAGT	GGCACTGGCT	GGTTTCGCTA	CCGTA
A	NF	PS			
L	RN	VA			
U	UU	UU			
1	12	1A			

120	130	
GCGCA	GGCCTCTGGT	AAAAGCTT
H	S H M	HA
H	T A N	IL
A	U E L	NU
1	1 3 1	31--

Please replace paragraph [0120], with the following paragraph:

C19

--[0120] Linker B1 (SEQ ID No: 19) is: GATCCCAGGCCTGCA--

Please replace paragraph [0121], with the following paragraph::

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C20

--[0121] Linker B2 (SEQ ID No: 20) is: GGCCTGG--

Please replace paragraph [0136], with the following paragraph:

C21

--[0136] The second preferred sequence (SEQ ID No: 6) as set forth herein, i.e.,

10            20            30            40            50            60  
GGCCATGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTT  
  
70            80            90            100          110          120  
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC  
  
130          140          150          160          170          180  
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG  
  
190          200          210          220          230          240  
TTCGTGGGGA CACCAGAAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG  
  
250          260          270          280          290          300  
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC  
  
310          320          330          340          350          360  
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG  
  
370          380          390          400          410          420  
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCGTG  
  
430  
GCTCCCTGGA AC--

**IN THE CLAIMS:**

Please cancel claim 26 without prejudice or disclaimer. Please amend claim 25, as follows:

25. (Amended) A purified collagenase inhibitor protein, said protein consisting essentially of an amino acid sequence selected from among the following:

a) amino acid sequence SEQ ID NO: 2; or

b) the amino acid sequence of a) or of SEQ ID NO: 1, further having a Met at position -1; or

c) the amino acid sequence of a) or of SEQ ID NO: 1, further having a leader sequence at the N-terminal, -1 position, wherein said leader sequence consists essentially of the following amino acid sequence from positions -38 to -1:

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C21  
cont

C22